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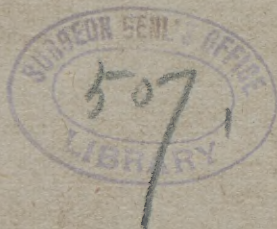
*Its Origin, Development, and Histological
Position.*

BY

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ITS ORIGIN, DEVELOPMENT, AND HISTOLOGICAL POSITION.

By W. C. BORDEN, M.D.,

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THE apparent simplicity of development of the fat cell would seem to make the task of tracing it back to its original cell form, and so determining its origin, an easy one. That this is not the case is evinced by the fact that observers are still far from agreeing what its original cell form really is. Of the many views advanced, those which assign its origin to some form of connective-tissue cell are most widely accepted and almost exclusively presented by writers upon histology and physiology.

My investigations, however, have led me to believe that these views are incorrect, and that they have given rise to erroneous ideas concerning the histological and physiological position of the fat cell.

As the facts which have led me to these conclusions are derived from observations upon fat tissue in foetal and adult, higher and lower vertebrates; it will be necessary to briefly summarize the facts of histology, embryology,

and comparative anatomy relative to the form and occurrence of this tissue.

Fat tissue, or adipose tissue, as it is generally technically called, consists of aggregations of the distinctive fat cells bound together by a small amount of connective tissue and of the necessary vascular, lymphatic, and nervous supply. In the higher vertebrates it is found in various parts of the body in masses of all manner of sizes and shapes adapted to the various situations. The larger masses are divided by intervening connective-tissue *sæpta* into lobes, and these lobes are in like manner subdivided into lobules. The blood supply is very abundant. Each lobule has an afferent arteriole which subdivides into a meshed capillary network, the capillaries again uniting into an efferent vein (Fig. 1).

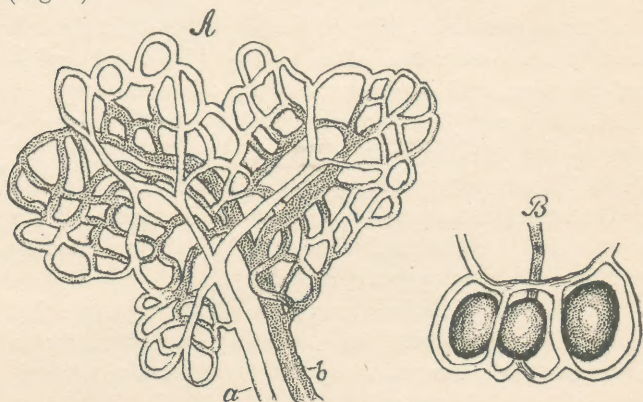


FIG. 1.—Vessels of the fat cell. A, arterial (α) and venous (β) branches, with the capillaries between them; B, the capillaries around three cells. (Frey.)

Even in the intermuscular spaces and like places where adipose tissue occurs as groups of cells having no distinct lobular formation, a capillary reticulum is present; and whenever a new formation of fat cells takes place, a more

or less distinct capillary network is developed, according to whether the formation consists of few or many cells. The resemblance between the vascular supply of adipose tissue and that of the secreting glands—such as the parotid, pancreas, and others—is most marked; for in all the vascular supply is abundant and is so distributed that each cell, whether it be parotid, pancreatic, or adipose, is in direct relation with one or more capillaries. This gland-like blood supply of adipose tissue is important when considering the histological position of this tissue, and will be again referred to farther on.

While adipose tissue is scattered through the body in the higher vertebrates apparently without design, this is not really the case, for certain regions are particularly characterized by its presence, and in others it never occurs. It is particularly abundant in the subcutaneous connective tissue, the omentum, around the kidneys, and notably in the hump of camels, which latter consists of a large fat deposit and is not in any way due to a deviation of the vertebral column. On the other hand, although connective tissue is abundantly present, fat tissue never occurs in the eyelids, penis, scrotum, nymphæ, submucous tissue of the intestine, or cavity of the cranium. Of these, the most notable instance of the limitation of fat extension is furnished by its absence from the submucous layer of the intestines, to which it never extends, though it is abundantly present in the mesentery, and at the junction of the latter with the intestine the fat deposits in it are separated from the submucous tissue of the intestine by the thickness of the muscular walls of the intestine only.

In the lower vertebrates adipose tissue is not scattered through the body at all, but is confined to certain definite localities where it is collected into gland-like bodies called "fat bodies," or "corpora adiposa." In the frog, the fat

bodies are in the abdominal cavity in close relation with the genito-urinary organs. In the necturus there are subcutaneous fat tracts on the dorsal and ventral parts of the body. In the toad, besides two abdominal fat bodies like those of the frog, there is an accumulation of fat about the base of the heart, and there are six fat bodies beneath the skin on the ventral surface of the body—one at the junction of each limb with the body and two at the base of the neck. It may be considered that the intra-abdominal fat bodies of the frog are homologous with the fat masses about the kidneys of higher vertebrates, and that the subcutaneous fat tracts of the necturus and the subcutaneous fat bodies of the toad are homologous with the panniculus adiposus of higher vertebrates. It at first appears somewhat strange that while in the lower vertebrates adipose tissue is confined to certain localities, there being formed into ductless glands, as we rise in the animal scale it is not so confined, but is scattered through the body apparently in a much less purposive way. This is seemingly at variance with the general rule that segregation of like tissues is coincident with higher development. This rule, however, of necessity yields to the requirements of the organism; and the following is suggested as a probable reason why fat tissue occurs in different localities in different animals and is scattered through the body in higher vertebrates, instead of being confined to definite localities, as in the lower.

In the lower vertebrates the amount of adipose tissue relatively to the size of the entire body is small; but *pari passu* with the rise in the animal scale the relative amount of adipose tissue increases, until in the higher vertebrates its proportion to the body is large. If the fat tissues of a mammal—man, for instance—were collected into two abdominal organs, as in the frog, the abdomen would have

to be enormously increased in size in order to contain them, and such localized deposition of the fat tissues would greatly, if not vitally, interfere with the existence of the organism. In fact, the localized deposition of the fat tissues, if adhered to in vertebrates, would prevent in the higher types that symmetrical development of the body which is so necessary to bring it into proper relations with its environment. It appears obvious, therefore, that as the more highly developed organisms were evolved, requiring increased amounts of adipose tissue for nutritive purposes, the only way to dispose of the increased tissue was to distribute it throughout the body, filling in the connective-tissue interspaces and spreading it out in the panniculus adiposus, for in this way only could it be so co-ordinated with the body as not to interfere with organic existence or symmetry.

As the spaces filled in were those previously occupied by connective tissue, it was natural to infer that that tissue was changed into adipose tissue. This view has been strengthened by observations on starved and fed animals and on the development of fat cells in connective-tissue spaces until the theory that fat cells are developed from connective-tissue cells has gained wide credence. So high an authority as Schäfer, in the last (tenth) edition of Quain's *Anatomy*, vol. i, part ii, page 237, says: "It (fat) is deposited in the form of minute granules or droplets in certain cells of the connective tissue"; and Foster, in the sixth and last edition of his *Physiology*, part ii, page 770, writes: "It is obvious that a fat cell is a cell belonging to connective tissue, in the cell substance of which fat has collected. . . ." But, notwithstanding the seeming conclusiveness of such statements, my investigations have led me to the belief that they are based upon incorrect data, that they do not assign a proper or sufficiently important

place to the fat cell, and that *the fat cell is a special cell having nothing in common with connective tissue, and that it is essentially a gland cell having special metabolic functions.* In support of this conclusion, the facts of comparative anatomy, embryology, and physiology relative to adipose tissue must be considered; and, in addition, the form of the fat cell at *all* stages of its existence must be known and taken into account.

The fat cell in its fully developed and functionally active state may be described as a protoplasmic, nucleated sac, the cavity of which is filled by a single drop of fat. The nucleus is about 7μ in diameter, and near it the cell protoplasm is thicker than at other parts surrounding the fat. A cross section of such a cell through the nucleus has been likened in appearance to a signet ring—the signet representing the nucleus; the thickened metal setting of the signet, the accumulation of protoplasm about the nucleus; and the thinner band, the extremely thin protoplasm covering the fat drop (Fig. 2, C).

The fat cell is developed into this form from a cell entirely free from fat. The fat is secreted in the cell in gradually increasing quantity by the metabolic action of the cell until the nucleus is displaced laterally by the increasing fat and the distended cell assumes a nearly globular form. But while this is the form of the fully developed cell during nutritive activity in the body of a well-nourished vertebrate, its original fat-free form is very different. What the original form is can not be said to be definitely settled. Observers who maintain for it a connective-tissue origin have described and figured it both as a branched and as an unbranched cell, and have described it as arising from the formed and from the granular unbranched cells of that tissue; others have described it as arising from lymphoid or special plasma cells. Where such diversity of

opinion exists, it is obvious that there is opportunity for further investigation; and it is equally obvious that the real origin and original form of the cell must be known before its histological and physiological position can be accurately assigned.

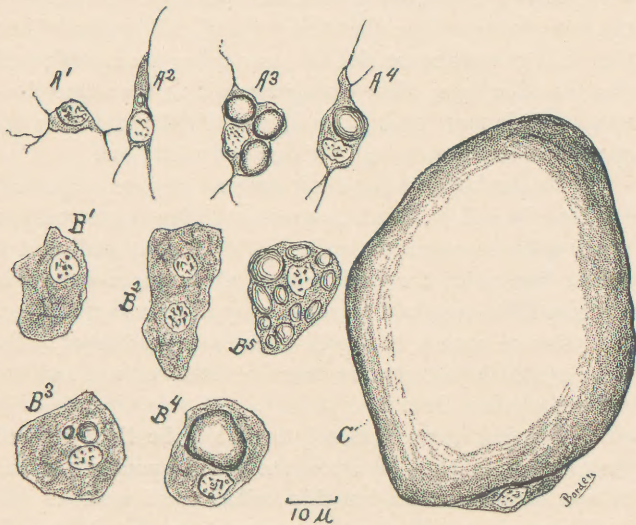


FIG. 2.—Developing and fully formed fat cells and the two types of cell from which fat cells originate. A^1 to A^4 , development from the so-called connective-tissue-cell form; B^1 to B^5 , development from the gland-cell form; B^2 , gland-cell form with two nuclei preparatory to cell division; A^2 to A^4 , B^3 to B^5 , cells with single and multiple deposits of fat; C, fully developed fat cell. All drawn to same scale with Zeiss's 2-millimetre oil-immersion apochromatic objective and Abbé's camera lucida.

The results of my investigations upon these disputed points are contained in this article, and, as regards the origin and original form of the fat cell, may be formulated as follows:

1. That in the lower vertebrates the fat cell is developed

from *one* form of cell, and that cells of this form are developed from special centers in the embryo.

2. That in the higher vertebrates fat cells are developed from *two* forms of cells differing greatly in size and shape.

3. That one of the original fat-cell forms in the higher vertebrates is homologous with the special-center forms of the lower vertebrates; that this form of cell is gland-like; that it in no way resembles the connective-tissue cell; and that the other form, while closely resembling the connective-tissue cell, is most probably a special cell, derived from the special-center form by cell division and migration.

If the fat bodies of an adult summer frog are examined, the fat cells will be found to present all the characteristics of the fully developed fat cell; but if the fat bodies of a winter frog which has used up most of its stored-up fat are examined, the cells will present a very different appearance. A section of such a body will show a collection of cells, some of which still contain more or less fat, while others are entirely free from it.

Those free from fat closely resemble the liver cells of the same animal. Between the closely packed fat-free cells nothing is visible but thin-walled blood-vessels. Fat bodies of almost identical appearance are found beneath the skin of foetal higher vertebrates. The panniculus adiposus and the fat about the kidneys of mammals have their origin in such bodies. They are seen as rather regularly shaped, gland-like masses, and may be easily found and studied in the foetal cat at term.

Those beneath the skin first appear on the ventral surface of the body, in the axilla and groin, the regions to which subcutaneous fat is limited in certain of the lower vertebrates.

It will be seen from this that the foetal cat resembles the adult toad, for both have fat glands in close relation

with the kidneys and localized beneath the skin on the ventral surface of the body near the limbs; and that this is in strict accordance with the rule that the foetal forms of the higher vertebrates resemble the adult forms of the lower.

Fig. 3, from a photomicrograph of a section through the skin of a kitten at term, shows the gland-like masses of fat cells beneath the skin, and Fig. 4 shows distinctly the gland-like form of these cell accumulations. The cells composing these masses are irregularly polyhedral in form and of large size, being from 15μ to 20μ in diameter (Fig. 2, B¹ to B³, and Fig. 5). The nucleus, which measures about 7μ , is central, or nearly so, and in many cells can be seen to be in active caryocinesis preparatory to cell division (Fig. 2, B²). The growth of the masses is by means of indirect cell division, the development of the capillaries going on coincidently with that of the cells, as is the case in all gland development.

In the masses the cells will be seen to be in many different degrees of fat accumulation, some entirely without fat, others containing many fat droplets still separated from each other by intervening cell protoplasm, while in others the fat drops have coalesced into one and the cell nucleus has been more or less displaced laterally.

How utterly unlike these cells are to connective-tissue cells is fully shown in Fig. 5 (from a photomicrograph) and in Fig. 2, B¹ to B⁵, drawn with Abbé's camera lucida from the young developing cells of the fat bodies. The central cell in Fig. 5 is a typical fat cell of the gland-cell form before fat formation has commenced. As the focus, when the photomicrograph was taken, was adjusted to give a critical image of this cell, the neighboring cells are somewhat blurred from the objective not being perfectly aplanatic, but it may be seen that they have the same general form and that some of them contain small fat drops. The ex-

istence of this distinctive gland-cell form of young fat tissue can be easily demonstrated upon any foetal mammal of suitable age.

So far as I have been able to determine, this origin of fat cells from gland-like cells in gland-like masses occurs only in the lower vertebrates and in the *foetal* forms of the higher. In the lower vertebrates it is the only way by which fat tissue originates. In the higher vertebrates, while its first appearance is in special centers with these gland-like cells, a *secondary* origin also obtains. Undoubtedly it is this origin which has given rise to the theory of the connective-tissue origin of the fat cells, for the cells from which fat cells secondarily originate, before any fat is deposited in them, closely resemble connective-tissue cells. But, notwithstanding this resemblance, it is probable that they are cells formed by cell division from the original special-center cells, and that they, by cell migration, form metastatic fat masses in places where fat tissue does not occur in the lower vertebrate types. It is from this secondary form of migrated embryonal fat cell that all fat tissue outside the special-center masses is developed. In this way originates the fat tissue of the omentum and mesentery, that between the muscular layers, and in the many other parts of the body where it appears after or late in foetal life.

The method of development is for a few of these secondary fat-cell forms to appear in the connective-tissue spaces alongside an already formed blood vessel. A capillary loop develops around these cells, other fat cells form outside this loop, another loop forms inclosing these, and so on, until a more or less distinct lobule of adipose tissue is formed. As it is by this process that new and scattered fat formations occur in the higher vertebrates after birth, it is the one most commonly and easily seen, and has, there-

fore, been generally considered the sole method by which fat tissue originates. It may be fairly well studied in the broad ligament of pregnant mammals; and if such studies were exclusively relied upon, an observer might well consider the connective-tissue origin of fat tissue established. But, like many other disputed questions in histology, the facts of embryology and comparative anatomy must be ascertained before right conclusions can be reached. If we examine a foetus of right age, or a lower vertebrate, fat cells, forming in special centers from large polyedral cells only, will be seen; while if we examine an older foetus of a higher vertebrate, the secondary method will be seen going on, together with the original method. For instance, if a section of the skin of a foetal cat at term is made through the subcutaneous fat masses in the groin or axilla, as in Fig. 3, in addition to the gland-like cell masses, cells will be found close to the hair roots and capillaries in the bodies of which fat is being deposited. These cells closely resemble connective-tissue cells and are the second form from which fat cells are developed in higher vertebrates (Fig. 2, A' to A⁴, and Fig. 6).

These cells are much smaller than the special-center forms and of a different shape. They are from $12\ \mu$ to $20\ \mu$ long, but are only a little wider than their nucleus, which, like that of the special-center forms, is about $7\ \mu$ in diameter. Fat first appears in the cell in one or more minute drops, generally not more than three. As these fat drops increase in size the cell protoplasm (spongioplasm) between them gives way, they run together, forming a single drop which increases in size and displaces the nucleus laterally until the usual form of the fully developed fat cell is obtained (Fig. 2, C). When young—*i. e.*, when fat first appears in them—these cells have processes similar to those of the formed (fixed) connective-tissue cells, though some

observers have described them as having none. Had they none, their dissimilarity to connective-tissue cells would be more marked, but processes are always present by the time the cell has become stationary and fat formation has begun. The seeming absence of processes is due to the difficulty of so staining them that they and their connections to particular cells can be plainly made out. They are best shown in thin sections from tissue hardened in Müller's fluid or osmic-acid solutions and imbedded in paraffin, the sections fastened to the slide and deeply stained with Weigert's hæmatoxylin. The sections should be fixed to the slide without cement, otherwise the cement might become stained, so, possibly, giving erroneous pictures. To fix the section properly, a slide is cleaned with a solution of caustic potash to insure freedom from any trace of grease, a drop of water is then put on the slide, the section placed on the water, and the slide placed in the oven of a water bath at 42° C. until all wrinkles have disappeared from the section. The water is then drained off, bringing the section into close contact with the slide, and the slide is then replaced in the oven and kept there at the same temperature as before for twelve hours. The albumin of the section will so fix it to the slide that it may be cleaned of the paraffin and stained in the usual way.

Fig. 6, from a photomicrograph of a section so treated, shows one of the secondary forms from which fat cells develop. Similar cells are found wherever adipose tissue is developing outside the special-center cell masses. Comparison of the cell shown in Fig. 5 with the one shown in Fig. 6 will show most plainly the difference between the two kinds of cells from which fat cells originate. In comparing these figures it must be noted that the amplifications are different, the relative size of the cells being shown in Fig. 2, A¹ and B¹, where they are drawn to the same scale.

So far as the first, or gland-cell form, of the fat cell is concerned, there can be no question as to its entire dissimilarity to the connective-tissue cell; but, as regards the second or metastatic form, it is so similar in form to certain cells of the connective tissue that absolute proof that it is not such a cell is difficult and must rest at present upon the circumstances connected with its first appearance and upon its subsequent function. I have already stated that this second form probably arises by cell division from the first form, and by migration forms new centers for fat-tissue formation. As fat cells are specialized cells, having special and important metabolic functions to perform, and as their original forms are developed from special cells, both in the lower vertebrates and in the embryos of the higher, it is natural to infer that all fat-cell forms have a similar origin. All special tissues arise from embryonal tissues by gradual differentiation, and when they have once reached a highly specialized form, change of form and function does not normally occur. Between cells having metabolic functions and those having supporting functions there is a wide difference, and, with the exception of the fat cell, it is generally considered established that cells having anabolic and catabolic action in nutritive processes do not change their functional form during development. If fat tissue is an exception to this general rule, it is certainly a curious anomaly.

Physiologists have fully demonstrated that fat is formed by the fat cells from substances other than ingested fat. The importance of this physiological action of the fat cells is emphasized by the great vascularity of adipose tissue, which shows that it is an active tissue physiologically; so that, both by its function and its blood supply, it closely resembles the glandular tissues. These facts are of much more importance when considering its true histological and

physiological position than is the absence of excretory ducts, for in all these particulars adipose tissue is very like the liver as regards the glycogenic function of that gland. The liver forms glycogen from substances other than ingested sugar and gives it to the organism either as glycogen or in different form. In this function the liver is a ductless gland; the blood-vessels supply the cells with the material for metabolic change and carry away the product formed and given out. In like manner adipose tissue is supplied by its network of capillaries. Not only does the fat cell form fat, but it afterward disposes of it. Although the fully developed fat cell is so distended with fat that its protoplasm is reduced to a thin covering for the fat, it is still functionally active, and is not only capable of forming fat, but it returns the formed fat to the blood either as fat or in some other form. This inverse action requires fully as special metabolic function and activity as is required for the formation of the fat, for according to the varying demands of the system, so must the various fat cells give out the proper supply. In hibernating animals during the hibernating period, the consumption of fat and the consequent inverse metabolic action of the fat cells must be very carefully adjusted to the requirements of the body and to the length of the hibernating period.

The slow physiological giving out of fat is the true fat-reducing method and differs from starvation in that the latter is an entirely pathological process. It is stated by some observers that the fat cells of a starved animal return to a connective-tissue form. This is undoubtedly an erroneous interpretation of structure. I have never been able to obtain the adipose tissue of a hibernating higher vertebrate during the hibernating period for examination, but in the frog the cells of the corpora adiposa never become connective-tissue cells. As the fat gradually disappears from

them during the winter months, they gradually return to their original cell form. In this they closely resemble liver cells, for fat is often found in the latter; and when discharged, the cells return to their former shape. In starvation, however, the case is different. Then the fat is so rapidly given out by the distended adipose cells and their own nutrition is at the same time so interfered with that they have no opportunity to return to their original form. The cell walls fall toward each other like the walls of an emptied bag and in sections of tissue give an appearance much like that of connective-tissue fibers. But the cells have not become connective-tissue cells; they are only the shrunken and wrinkled, pathologically changed, fat cells. All the fat does not disappear from all the cells, even in extreme emaciation, and those cells devoid of fat still contain a yellowish fluid whose color is derived from the discharged fat. That they retain the coloring matter of the fat while they discharge the fat itself is entirely at variance with the supposition that they become connective-tissue cells.

Finally, if nutrition is resumed in a previously starved animal, all the fat cells again fill with fat without going through the process of development characteristic of their original development, and which would have been necessary had they assumed a connective-tissue-cell form.

We have the following, therefore, in support of the special cell origin and glandular nature of the fat cell:

1. Its occurrence in the lower vertebrates in special organs, composed of gland-like cells, developed from special centers.

2. Its first appearance in foetal higher vertebrates in gland-like masses, developed from special centers, homologous with the special fat organs of the lower vertebrates.

3. The continuance of adipose tissue in the lower vertebrates as fat glands, never changing into other tissue, and

as distinct in structure and function as other ductless gland tissue.

4. The limits placed upon the place of occurrence of adipose tissue in all animals, and its non appearance in certain regions where connective tissue is always present.

5. Its specialized metabolic functions, and the gland-like development and arrangement of its blood supply, all of which place it in an entirely different histological and physiological class from that of the supporting functioned connective tissues.

Bibliography.—The bibliography is extensive, and up to 1887 is collected in a paper by Gage: Fat Cells and Connective-tissue Corpuscles of Necturus (*Menobranchus*), published in the *Proceedings of the American Society of Microscopists*, vol. iv, for that year. Of later date, Foster's *Physiology*, 5th edition, part ii, gives a most excellent account of the physiology of fat tissue; and Schäfer, in Quain's *Anatomy*, tenth edition, vol. i, part ii, gives a full account of the origin of the fat cell according to the connective-tissue cell theory.

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EDITED BY

FRANK P. FOSTER, M.D.

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